Presidenza del Consiglio dei Ministri

COMITATO TECNICO-SCIENTIFICO
Ex O.C.D.P.C. 3 febbraio 2020, n. 630, come modificata dalla O.C.D.P.C. 17 marzo 2021, n. 751

Verbale n. 39 della riunione tenuta presso il Dipartimento della Protezione Civile il giorno 5 agosto 2021

	Presente	Assente
Franco LOCATELLI (coordinatore)	in videoconferenza	
Silvio BRUSAFERRO (portavoce)	in videoconferenza	
Sergio FIORENTINO (segretario)	in videoconferenza	
Sergio ABRIGNANI	in videoconferenza	
Cinzia CAPORALE	in videoconferenza	
Fabio CICILIANO	in videoconferenza	
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Giuseppe IPPOLITO	in videoconferenza	
Alessia MELEGARO	in videoconferenza	
Giorgio PALÙ		X
Giovanni REZZA	in videoconferenza	

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Ordine del giorno, di cui alla nota di convocazione del 29 luglio 2021:

1. Quesiti circa le misure di prevenzione e protezione dal rischio di contagio nel settore dei trasporti;

2. Valutazione della regola della quarantena precauzionale nei soggetti che hanno avuto contatti con una persona contagiata, ma che abbiano completato il ciclo vaccinale.

3. Condizioni di eventuale rilascio del c.d. green pass per uso domestico ai soggetti residenti nella Repubblica di San Marino che abbiano completato il ciclo vaccinale con il vaccino di fabbricazione russa Sputnik.

4. Varie ed eventuali.

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La seduta inizia alle ore 8,05.

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In apertura di seduta, anticipando l'esame di una delle questioni varie ed eventuali, il Coordinatore ritiene necessario ritornare su uno degli argomenti esaminati nella scorsa seduta del 30 luglio 2021, relativo alla condizione delle persone che hanno partecipato alla sperimentazione del vaccino sviluppato dalla società ReiThera, ai fini dell'ottenimento del green pass.

Nelle more della seduta odierna, la Direzione generale della prevenzione del Ministero della Salute ha appreso che, ad un certo numero dei partecipanti alla sperimentazione, è stata somministrata una dose unica di vaccino, contenente il doppio del quantitativo rispetto a quello della singola dose nel ciclo di due.

Secondo i ricercatori che hanno partecipato alla sperimentazione, non vi sarebbero evidenti differenze nei dati laboratoristici relativi alla risposta immune dei soggetti che hanno ricevuto le due dosi (per i quali il CTS, nella seduta del 30 luglio u.s., ha ritenuto possibile concedere un'esenzione ai fini dell'ottenimento del green pass) e dei soggetti che hanno ricevuto la dose di misura doppia. Queste valutazioni non hanno, tuttavia, formato oggetto di studi pubblicati e verificabili.

Ritiene, pertanto, il CTS che, ai fini della concessione della suddetta esenzione, non possa considerarsi sufficiente la singola somministrazione, benché di dose doppia, del vaccino sperimentato da ReiThera, essendo a tal fine necessaria la somministrazione una ulteriore dose di vaccino diverso, approvato dalle agenzie regolatorie nazionali o dell'Unione europea.

Con l'occasione, il CTS ribadisce che le ragioni per le quali si è ritenuta praticabile la soluzione dell'esenzione risiedono nel particolare favore con il quale va considerata la scelta dei volontari che hanno partecipato alla sperimentazione, anche al fine di non scoraggiare la partecipazione di volontari a future sperimentazioni. IL CTS ritiene, inoltre, di sottolineare che queste ragioni non implicano in alcun modo l'esistenza di evidenze che supportino un giudizio di equivalenza, dal punto di vista della copertura

immunologica, tra la condizione di chi ha completato il ciclo vaccinale con uno dei vaccini approvati dalle Agenzie Regolatorie e quella di chi ha completato il ciclo vaccinale sperimentale di ReiThera. Il CTS ritiene di raccomandare che questa precisazione venga esplicitata ai diretti interessati.

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Il CTS passa, quindi, ad esaminare i quesiti oggetto della richiesta di parere formulata con nota in data 4 agosto 2021 dal Segretario Generale della Presidenza del Consiglio dei ministri (allegato).

Con il primo di essi (punto 2 dell'ordine del giorno), si chiede al Comitato se la regola della quarantena precauzionale applicabile ai soggetti che hanno avuto contatti stretti con casi confermati di SARS-CoV-2 possa essere modificata nell'ipotesi in cui le persone venute a contatto con un soggetto contagiato abbiano completato il ciclo vaccinale.

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All'esito di approfondita discussione, il CTS rileva che la protezione dall'infezione da SARS-CoV-2 conferita dalla vaccinazione, in base ai dati diffusi dall'Istituto Superiore di Sanità, si attesta, allo stato delle evidenze scientifiche, sull'88% [dato sostanzialmente confermato da tutti gli studi internazionali: v. allegata tabella *Studies to date that showed COVID-19 vaccines reduce asymptomatic infection (transmission)*]. Due recenti studi condotti in Israele, con riferimento al vaccino Comirnaty (*Matan Levine-Tiefenbrun e altri: Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine* – allegato), e nel Regno Unito, con riferimento al vaccino Vaxzevria (Ross J. Harris: Effect of Vaccination on Household Transmission of SARS-CoV-2 in England – allegato) indicano che vi è un ridotto rischio d'infezione che caratterizza i conviventi di soggetti che hanno completato il ciclo vaccinale, nel primo studio documentandosi anche una riduzione del carico virale in coloro che hanno sviluppato l'infezione 12–37 giorni dopo la prima

dose di vaccino. Inoltre, uno studio non ancora sottoposto a *peer-review* ma pubblicato su medRxiv (*PoYing Chia e altri: Virological and serological kinetics of SARS-CoV- 2 Delta variant vaccine-breaktrough infections: a multi-center cohort study* – allegato) fornisce evidenza che nei soggetti vaccinati che s'infettano si osserva un più rapido declino del carico virale rispetto ai soggetti che pure s'infettano, ma che non erano stati vaccinati, ciò determinando ridotta infettività.

Alla luce di quanto precede, ritiene il CTS, all'unanimità dei presenti, che vi siano le condizioni per differenziare il periodo di quarantena precauzionale, per i soggetti che hanno avuto contatti stretti con casi confermati di SARS-Cov-2, a seconda che tali soggetti abbiano, o meno, completato il ciclo di vaccinale, ritenendo, in particolare, che questo periodo possa per essi limitarsi a 7 giorni, a condizione che, alla scadenza di tale termine, venga effettuato un test diagnostico di esito negativo con uno dei tamponi connotati dalle caratteristiche di affidabile performance identificate nelle vigenti circolari del Ministero della salute.

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Con ulteriori due quesiti (punto 1 dell'o.d.g.), viene chiesto al CTS, con riferimento al trasporto pubblico locale, se il coefficiente di riempimento non superiore all'80% della capienza dei mezzi, attualmente vigente in base alle pertinenti Linee guida di cui agli allegati 15 e 18 del D.P.C.M. 2 marzo 2021, possa essere applicato anche nella c.d. "zona gialla" e se il rispetto della detta percentuale possa costituire misura sufficiente di prevenzione del contagio, senza che si debba prevedere l'ulteriore misura del distanziamento fisico di un metro tra i passeggeri o, eventualmente, con la previsione che tale ultima misura possa essere superata al raggiungimento di una data percentuale di popolazione vaccinata (anche Regione per Regione) ovvero adottando misure alternative.

Su tali punti, ritiene il CTS, all'unanimità dei presenti, che l'attuale situazione epidemiologica consenta di mantenere l'attuale limite di capienza dell'80%, alla condizione che se ne assicuri il rigoroso rispetto attraverso opportuni controlli, e che tale limite di capienza possa essere applicato anche nelle zone gialle, purché permanga l'obbligo di indossare un dispositivo di protezione individuale. Il CTS sottolinea, al riguardo, che la migliore protezione dal rischio di acquisire il contagio da SARS-CoV-2 è conferita dai dispositivi FFP2.

Il rispetto del distanziamento fisico di almeno un metro costituisce non obbligo stringente, ma utile raccomandazione, al cui rispetto, quando possibile, gli utenti del trasporto pubblico locale devono essere richiamati.

Tali indicazioni potranno essere eventualmente riviste al raggiungimento di una percentuale su base nazionale di almeno l'80% di soggetti che abbiano effettivamente completato il ciclo di vaccinazione rispetto alla popolazione dei residenti nel Paese. Ulteriori valutazioni potranno essere utilmente effettuate anche al mutare della situazione epidemiologica.

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Alle ore 9,20, considerato che diversi componenti hanno dovuto assentarsi per impegni istituzionali e che altrettanto dovrebbero fare a breve altri componenti, il Coordinatore dichiara chiusa la seduta, rinviando alla prossima riunione l'esame del punto n. 3 dell'ordine del giorno.

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Sergio ABRIGNANI[1]	in videoconferenza	
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Alessia MELEGARO[2]	in videoconferenza	
Giorgio PALÙ		X
Giovanni REZZA	in videoconferenza	

Verbale approvato dopo condivisione via e.mail da parte di tutti i Componenti.

IL COORDINATORE

Franco Locatelli

IL SEGRETARIO VERBALIZZANTE

Sergio Fiorentino

[1] Ha lasciato il collegamento alle ore 9,00.
[2] Ha lasciato il collegamento alle ore 9,00.

Il Segretario Generale
della Presidenza del Consiglio dei Ministri

Al Prof. Franco Locatelli
Coordinatore Comitato tecnico-scientifico
c/o Dipartimento della protezione civile

e, p.c. Al Pres. Goffredo Zaccardi
Capo Gabinetto del Ministero della Salute

All'Ing. Fabrizio Curcio
Capo Dipartimento della protezione civile

Oggetto: Quesiti rivolti al Comitato Tecnico Scientifico in ordine alle misure di prevenzione e protezione dal rischio di contagio nel settore dei trasporti e alla disciplina della quarantena precauzionale dei soggetti venuti a contatto con un caso confermato di SARS-Cov-2.

Al fine di organizzare e predisporre adeguate misure di prevenzione e protezione dal rischio di contagio nel settore dei trasporti, anche in considerazione dei progressi della campagna vaccinale, e al fine di meglio disciplinare la misura della quarantena precauzionale dei soggetti venuti a contatto con un caso confermato di SARS-Cov-2, si formulano a codesto Comitato Tecnico Scientifico i seguenti quesiti:

1) se la regola della quarantena precauzionale dei soggetti che hanno avuto contatti con casi confermati di SARS-CoV-2 possa essere modificata nell'ipotesi in cui i soggetti venuti a contatto con un individuo contagiato abbiano completato il ciclo vaccinale.

2) con riferimento al trasporto pubblico locale, se il coefficiente di riempimento non superiore all'80% della capacità dei mezzi, attualmente vigente in zona bianca in base alle "*Linee guida per l'informazione agli utenti e le modalità organizzative per il contenimento della diffusione del covid-19 in materia di trasporto pubblico*" e alle "*Linee guida per il trasporto scolastico dedicato*" (rispettivamente, allegato 15 e allegato 16 al decreto del Presidente del Consiglio dei Ministri adottato in data 2 marzo 2021), possa costituire una misura applicabile anche in zona gialla;

3) se il rispetto della predetta percentuale di capienza possa costituire una misura sufficiente alla prevenzione dal rischio di contagio senza che si debba prevedere l'ulteriore misura del distanziamento fisico di un metro tra i passeggeri, anche tenendo conto del raggiungimento, eventualmente Regione per Regione, di una determinata percentuale da definire di vaccinati rispetto ai soggetti vaccinabili, oppure adottando misure alternative.

Si chiede pertanto a codesto Comitato di esprimere un parere tecnico-scientifico sui quesiti sopra elencati.

L'occasione è gradita per porgere cordiali saluti.

Roberto Chieppa

Studies to date that showed COVID-19 vaccines reduce asymptomatic infection (transmission)		
Setting	Finding of xx% reduction in asymptomatic	Reference
Healthcare workers in England	86%	Hall SSRN, February 22, 2021
Healthcare workers in Israel	75%	Amit, Lancet, March 6, 2021
Patients in Mayo Clinic health system	88.7%	Pawlowski medRxiv, February 27, 2021
Israel Ministry of Health (nationwide)	94%	Pfizer press release, March 11, 2021
Israel general population (Pfizer)	90%	Dagan NEJM, February 24, 2021
Pre-surgical patients in Mayo Clinic system swabbed asymptomatically	80%	Tande Clin Inf Dis, March 10, 2021
Healthcare workers in Cambridge University Hospitals	75%	Weekes Authorea, February 24, 2021
Israel population (>16) with children unvaccinated	For every 20-point increase in adult vaccination, rates of kids testing positive halves	Milman O. Medrxiv. March 31, 2021
First-line responders and HCWs in US	90%	Thompson A. MMWR, March 30, 2021
Nasal viral load values are most important determinant of transmissibility (Lancet study); Nasal viral loads from post-vaccination exposures are low and likely noninfectious per CT values (use rapid antigen tests after vaccination if want to test symptomatic)		

BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-021-01316-7

nature medicine

Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine

Matan Levine-Tiefenbrun[1,6], Idan Yelin[1,6] ✉, Rachel Katz[2], Esma Herzel[2], Ziv Golan[3], Licita Schreiber[3], Tamar Wolf[3], Varda Nadler[3], Amir Ben-Tov[2,4], Jacob Kuint[2,4], Sivan Gazit[2], Tal Patalon[2], Gabriel Chodick[2,4] and Roy Kishony[1,5] ✉

Beyond their substantial protection of individual vaccinees, coronavirus disease 2019 (COVID-19) vaccines might reduce viral load in breakthrough infection and thereby further suppress onward transmission. In this analysis of a real-world dataset of positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test results after inoculation with the BNT162b2 messenger RNA vaccine, we found that the viral load was substantially reduced for infections occurring 12–37 d after the first dose of vaccine. These reduced viral loads hint at a potentially lower infectiousness, further contributing to vaccine effect on virus spread.

The recently authorized BNT162b2 Coronavirus Disease 2019 (COVID-19) messenger RNA (mRNA) vaccine is approximately 95% efficient in preventing polymerase chain reaction (PCR)-confirmed symptomatic disease from 7 d after the second dose and also provides some early protection starting 12 d after the first dose[1,2]. As countries race to vaccinate a substantial portion of their populations in the coming months, it is hoped that the basic reproduction number of the virus will decrease. This effect can be achieved by reducing the number of susceptible people, as well as by reducing viral load and, thereby, viral shedding of post-vaccination infections, which might render them less infectious[3–7]. However, the effect of vaccination on viral load in COVID-19 post-vaccination infections is currently unknown[8].

As of February 11, 2021, Maccabi Healthcare Services (MHS) in Israel has vaccinated more than 1 million of its members as part of a national rapid rollout of the vaccine. MHS member SARS-CoV-2 tests are often carried out in the MHS central laboratory, which offers the opportunity to track post-vaccination infections. In this study, we retrospectively collected and analyzed the quantitative reverse transcription PCR (RT–qPCR) test measurements of three SARS-CoV-2 genes—*E*, *N* and *RdRp* (Allplex 2019-nCoV assay, Seegene)—from positive post-vaccination tests performed at the MHS central laboratory between December 21, 2020, and February 11, 2021 ($n=4{,}938$ patients, study population; Table 1). The study period was characterized by high and steady rates of positive COVID-19 tests (Extended Data Fig. 1), indicating an ongoing epidemic wave.

In an analysis of the infection cycle threshold (Ct) over time, we found that the mean viral load substantially decreased 12 d after vaccination with the first vaccine dose, coinciding with the known early onset of vaccine-mediated protection[1]. When we calculated the mean Ct for post-vaccination infections identified on each day after vaccination, we found that the Ct values of positive samples collected 12–37 d after vaccination with the first dose (a second dose having been given on day 21 for all samples taken after day 21) were higher than the Ct values of positive samples taken during the first 11 d after vaccination for the *RdRp* gene (Fig. 1) and for the genes *N* and *E* (Extended Data Fig. 2) ($P<10^{-19}$ for the three genes, Mann–Whitney *U*-test). Differences in mean Ct calculated for these two time periods ranged from 1.7 ± 0.2 for *RdRp* to 1.6 ± 0.2 for gene *E* and 1.4 ± 0.2 for gene *N*.

Table 1 | Study population

Age group (years)	Total no. of patients	Male	Female
16–19	241	143	98
20–29	425	216	209
30–39	485	277	208
40–49	1,077	513	564
50–59	1,344	708	636
60–69	821	445	376
70–79	422	216	206
80–89	123	53	70

We next compared the Ct values of these post-vaccination infections with Ct values of positive tests of unvaccinated patients. All of the tests were of MHS members and were carried out at the central laboratory. Given that viral load could be associated with age and sex[9], we assembled control groups of positive tests in unvaccinated patients with matching age group, sex and sampling date range (Methods). Comparing the post-vaccination positive tests from days 1–11 ($n=3{,}050$) with their corresponding demographically and calendrically matched control group of the same size, we found no significant difference in the distribution of Ct values for *RdRp* (Fig. 2a and Extended Data Fig. 4a) or for genes *N* and *E* (Extended Data Figs. 3a and 4a). However, in a comparison of the Ct distribution for infections from days 12–37 after vaccination ($n=1{,}888$) with that of demographically matched unvaccinated control group infections ($n=1{,}888$), we identified a significant increase in Ct in vaccinated individuals (Fig. 2b for *RdRp* and Extended Data Fig. 3b for genes *N* and *E*; Mann–Whitney *U*-test, $P<10^{-10}$ for all three genes; Extended Data Fig. 4b,c). Finally, applied on all of the

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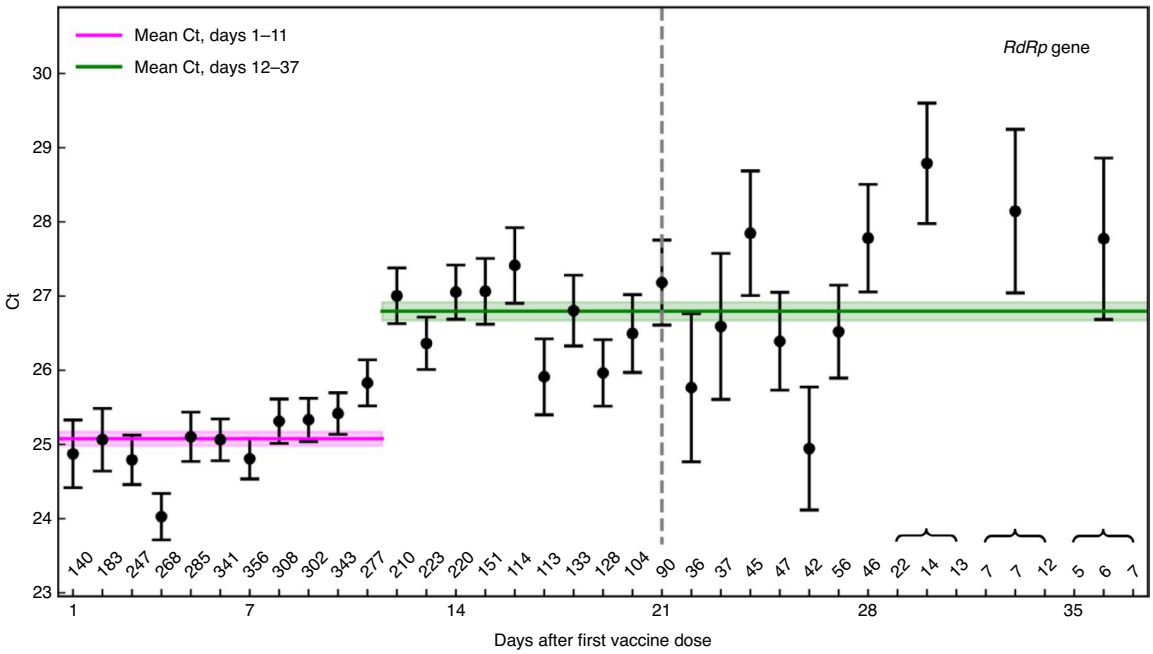

Fig. 1 | Decreased SARS-CoV-2 viral load after 12 d post-vaccination. Mean Ct values of the *RdRp* gene for positive tests after vaccination are plotted by the post-vaccination day in which the sample was taken. The dashed line on day 21 indicates inoculation with the second dose. The number of positive test results for each day is indicated below (in total, $n = 4{,}938$). Black error bars and green or magenta shading indicate the standard error of the mean. For days 29–37, each dot represents the mean of three consecutive days. For genes *E* and *N*, see Extended Data Fig. 2.

infections (post-vaccination and matched unvaccinated, $n = 9{,}876$), a multivariable linear regression model accounting for age, sex and vaccination found Ct regression coefficients ranging from 1.51 (*N* gene) to 1.76 (*RdRp*) for vaccination 12–21 d before infection sampling and even higher coefficients ranging from 1.90 (*N* gene) to 2.16 (*RdRp*) for vaccination 22–37 d before infection sampling (Fig. 2c for *RdRp* and Extended Data Fig. 5 for *N* and *E* genes; similar coefficients for independent models for each time bin are shown in Extended Data Fig. 6). Given that a difference of 1 Ct unit is approximately equivalent to a factor of 2 in the number of viral particles per sample, these Ct differences represent a decrease of 2.8–4.5-fold in viral load in vaccinated individuals.

Viral load has been shown to be associated with COVID-19 symptomatic disease as well as with time since infection[9–12]. To alleviate potential biases toward asymptomatic and/or long-term infections or persistent shedding in vaccinated participants, we repeated the multivariable linear regression analysis and restricted it to patients for whom a referral for COVID-19 testing was recorded ($n = 783$ vaccinees and the same number of demographically matched unvaccinated controls). For the linear regression model, these referrals were categorized into those indicating COVID-19 symptoms versus other causes for the test, mostly epidemiological contact tracing (0 and 1, asymptomatic and symptomatic). We found that symptomatic disease was indeed correlated with lower Ct values and that, when we adjusted for symptomatic infections, the association of vaccination with Ct remained (albeit with lower significance due to the reduced sample size of referral-based tests; Extended Data Fig. 7).

The results show that infections occurring 12 d or longer after vaccination have significantly reduced viral loads at the time of testing, potentially affecting viral shedding and contagiousness as well as the severity of the disease[13]. This report is based on an observational study, not a randomized controlled trial, and has several associated limitations. First, the group of vaccinees might differ from the demographically matched control group in ways that could affect the observed viral load, such as behavior, tendency to get tested and general health status. Second, the different viral variants, which could be associated with different viral loads, might affect different parts of the population. Third, by including only the first positive test for each patient, we attempted to minimize the effect of long-term, low-viral-load infections, but it is still possible that the association we observed, especially in the early post-vaccination days, reflects infections lasting from pre-immunization transmission events[9–12]. The average viral load might, therefore, continue to change in longer post-vaccination times, when infections are more strongly enriched for post-immunization transmissions, or due to change in vaccinee behavior, especially upon obtaining a vaccination certificate. Fourth, given that vaccines prevent symptomatic disease, post-vaccination tests might be enriched for cases of asymptomatic carriage characterized by lower viral load, although we note that the association of vaccination with low viral load remains even when adjusting for symptomatic disease (Extended Data Fig. 7). Finally, the oro-nasopharyngeal test does not distinguish the viral load in the nose from the one in the oral cavity and does not account for virus viability, which would be a better measure of potential infectiousness. Moreover, the infectious dose of SARS-CoV-2 in humans is presently unknown. The accumulation of wider and longer-term datasets, including contact tracing data as well as virus viability and genomics, will allow better quantification of the vaccine effect on infectiousness and its dependence on viral variants and vaccinee behavior. Nevertheless, at least for the conditions tested here, the lower viral loads that we observed could help fine-tune epidemiological models of vaccine effect on the spread of the virus.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-021-01316-7.

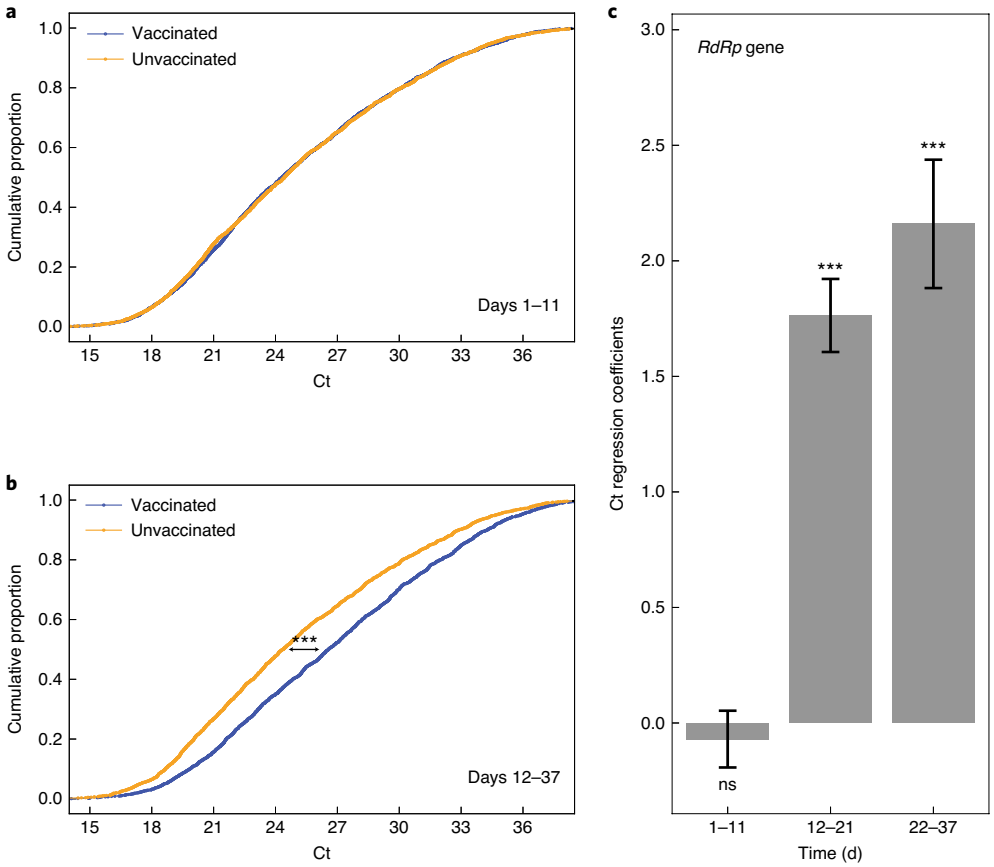

Fig. 2 | Comparison of SARS-CoV-2 viral loads among vaccinated and unvaccinated patients. a, **b**, The distribution of Ct values of the *RdRp* gene as determined for positive samples taken 1–11 d after vaccination (**a**, $n = 3{,}050$, blue) and 12–37 d after vaccination (**b**, $n = 1{,}888$, blue) with their respective demographically matched control groups (orange, $^{***}P < 10^{-17}$, two-sided Mann–Whitney *U*-test). For genes *E* and *N*, see Extended Data Fig. 3. **c**, Coefficient for the association of Ct of the *RdRp* gene with vaccination at different vaccination-to-sample time bins in comparison to unvaccinated patients as identified in a single multivariable linear regression analysis accounting for age and sex (Methods; $n = 9{,}876$). Error bars represent 1 s.d. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$. For genes *E* and *N*, see Extended Data Fig. 5a,b.

Received: 1 February 2021; Accepted: 9 March 2021;
Published online: 29 March 2021

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Methods

Data collection. Anonymized SARS-CoV-2 RT–qPCR Ct values were retrieved for all of the positive post-vaccination samples taken between December 21, 2020 (1 d after the first vaccine was administered) and February 11, 2021, and tested at the MHS central laboratory. Vaccination dates were retrieved from the centralized database of MHS. Patients were excluded if they had a positive sample before vaccination; if they had a positive sample more than 21 d after the first dose of the vaccine but did not receive the second dose on day 21; or if they were over the age of 90 years (28 patients older than 90 were not included because it was not possible to match them with unvaccinated controls). For patients with multiple positive post-vaccination tests, only the first test was included. For each test, Ct values for *E* gene, *RdRp* gene, *N* gene and the internal control were determined using Seegene proprietary software for the Allplex 2019-nCoV assay after the standard oro-nasopharyngeal swab specimen collection procedure. The same machine model, the Bio-Rad CFX96 Real-Time PCR Detection System, was used for all of the tests.

Unvaccinated patient control group. As a control group, for each post-vaccination SARS-CoV-2-positive patient, we used an algorithm to randomly choose an unvaccinated positive patient with similar characteristics (same sex and same age (in bins of 10 years)) and a similar date of first positive sample to account for possible calendric trends associated with the national state of the pandemic (nominally up to a 10-d difference, with this difference extended for 168 patients for whom we could not find matching unvaccinated controls) (Table 1).

Statistics. *Linear regression.* For each viral gene, we calculated the linear regression of Ct values as a function of sex (0/1, female/male) and age (linear, in years). Adding a quadratic age term was also tested, giving very similar results. Time after vaccination (one-hot encoded binary vector for time bins 1–11 d, 12–21 d and 22–37 d; unvaccinated were encoded as all-zero vectors). In an additional multivariable linear regression model, referral for COVID-19 test indicating symptoms was also included (0/1, asymptomatic/symptomatic). For this latter model, only patients for whom the positive test was by referral issued during the four previous days were included. Models were implemented using Python's statsmodels library, version 0.9.0.

Ethics committee approval. The study protocol was approved by the ethics committee of Maccabi Healthcare Services in Tel-Aviv, Israel (institutional review board (IRB) no. 0066-20-MHS). The IRB includes an exemption from informed consent.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

To protect patient privacy, underlying electronic health records may be accessed via a remote server pending a material transfer agreement. All other data are present in the paper.

Acknowledgements

This work was supported by the Israel Science Foundation (grant no. 3633/19 to R. Kishony and G.C.) as part of the KillCorona-Curbing Coronavirus Research Program.

Author contributions

Study design: M.L.-T., I.Y., T.P., S.G., G.C. and R. Kishony. Data collection: M.L.-T., I.Y., L.S., E.H., R. Katz, T.W., V.N. and Z.G. Data analysis: M.L.-T., I.Y. and R. Kishony. Data interpretation: M.L.-T., I.Y., J.K., L.S., T.W., V.N., A.B.-T., T.P., S.G., G.C. and R. Kishony. Writing: M.L.-T., I.Y. and R. Kishony, with comments from all authors.

Competing interests

The authors declare no competing interests.

Additional information

Extended data are available for this paper at https://doi.org/10.1038/s41591-021-01316-7.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-021-01316-7.

Correspondence and requests for materials should be addressed to I.Y. or R.K.

Peer review information *Nature Medicine* thanks the anonymous reviewers for their contribution to the peer review of this work. Alison Farrell was the primary editor on this article and managed its editorial process and peer review in collaboration with the rest of the editorial team.

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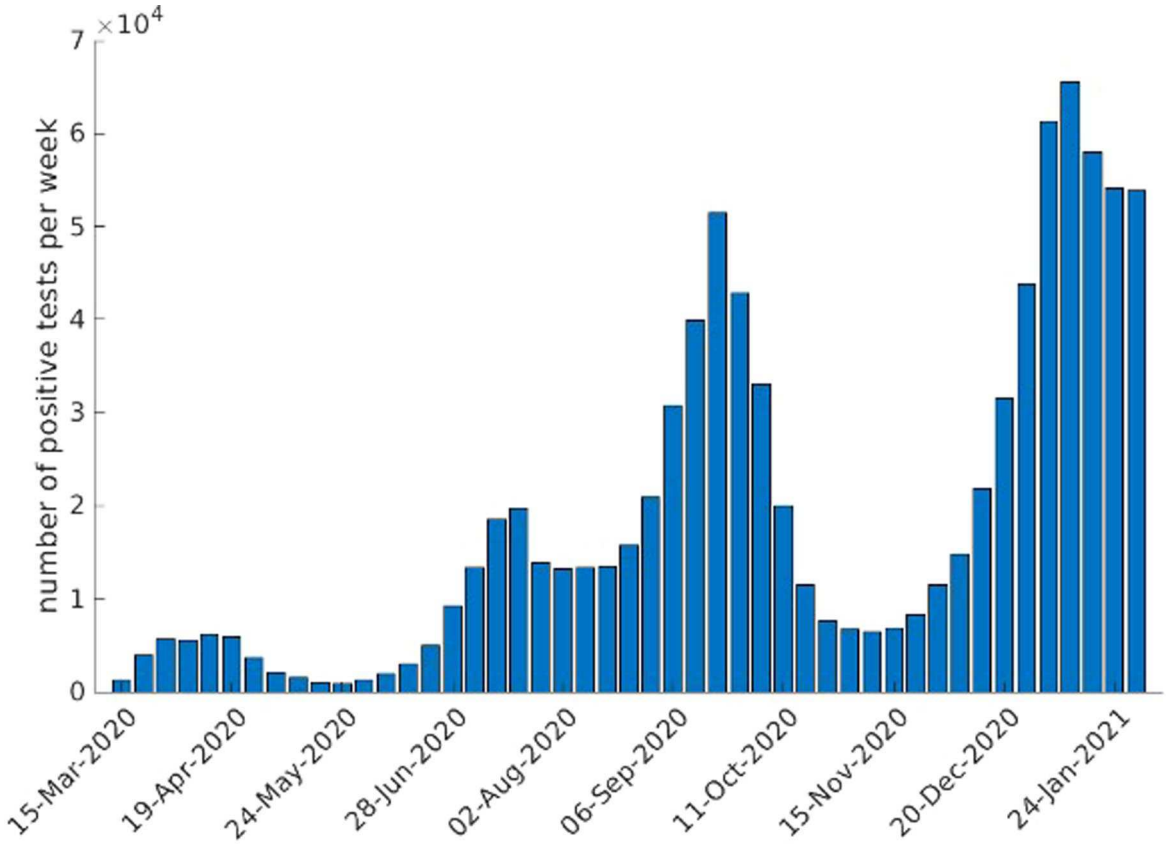
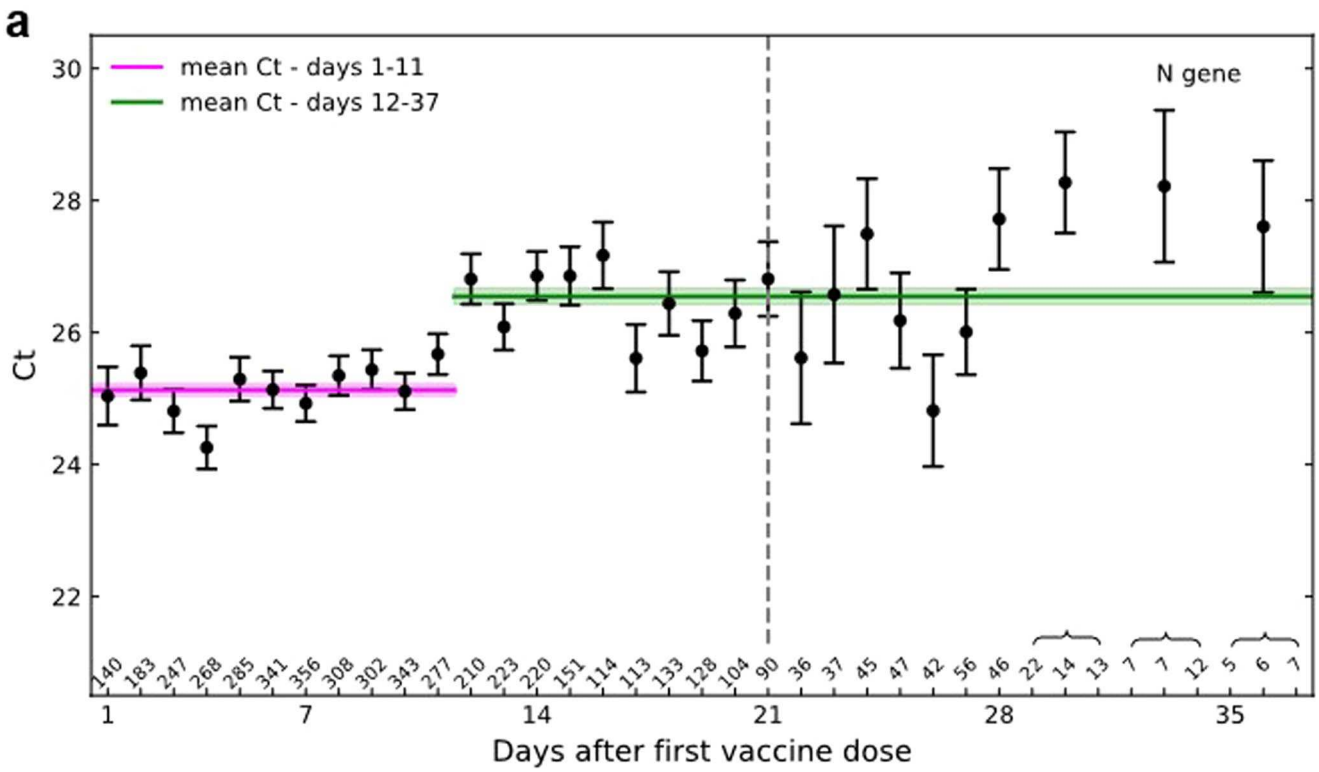
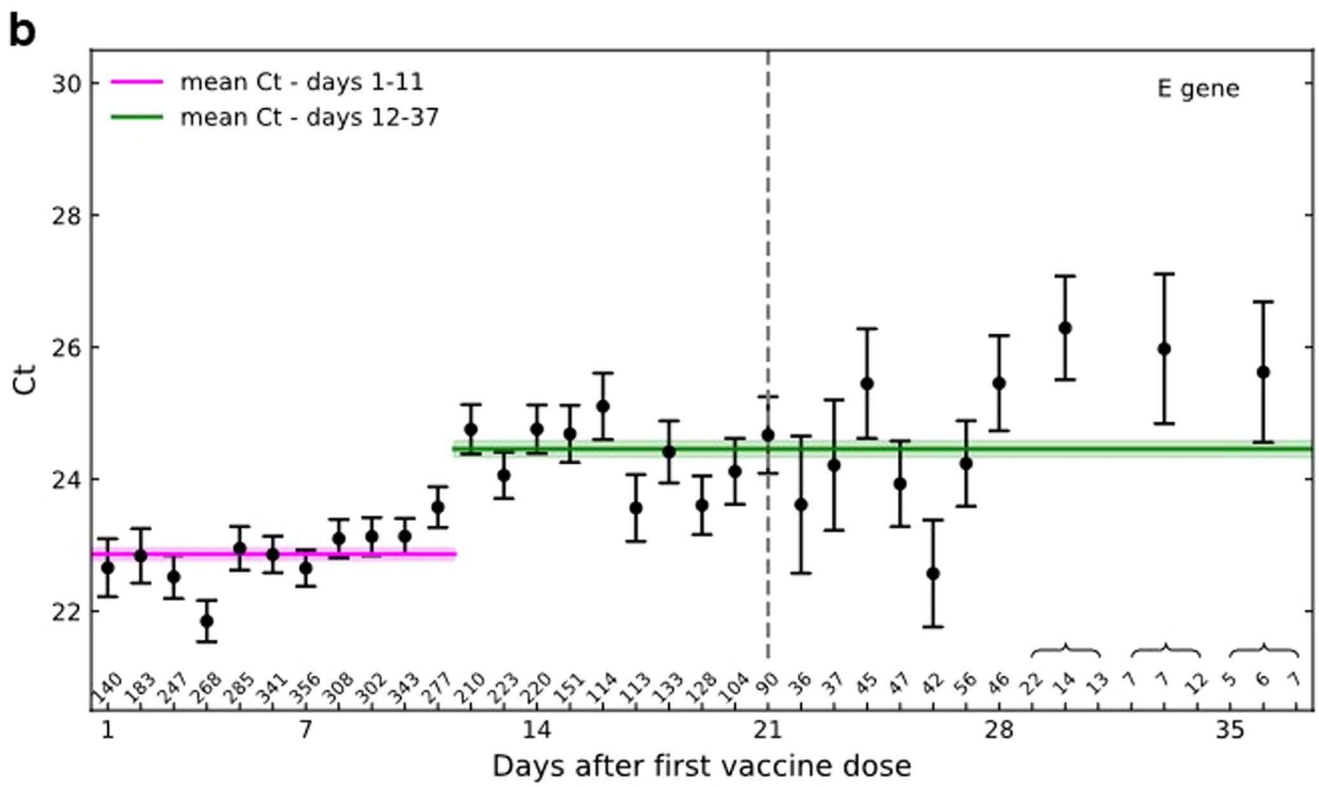
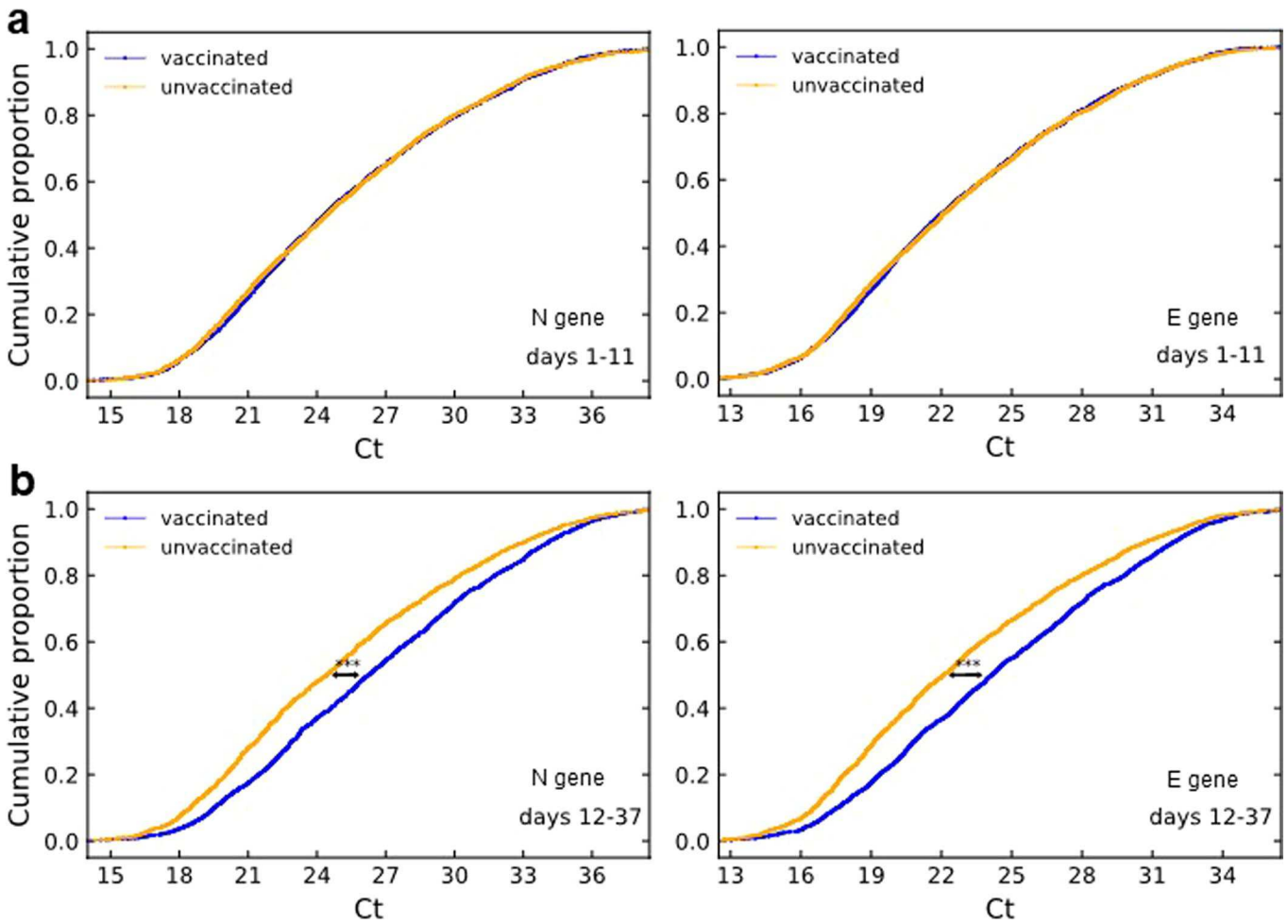


Extended Data Fig. 1 | Weekly positive COVID-19 tests in Israel. Total number of positive COVID-19 tests per week starting on March 15th 2020 and updated till February 11th 2021. Data retrieved from Israel Ministry of Health website.

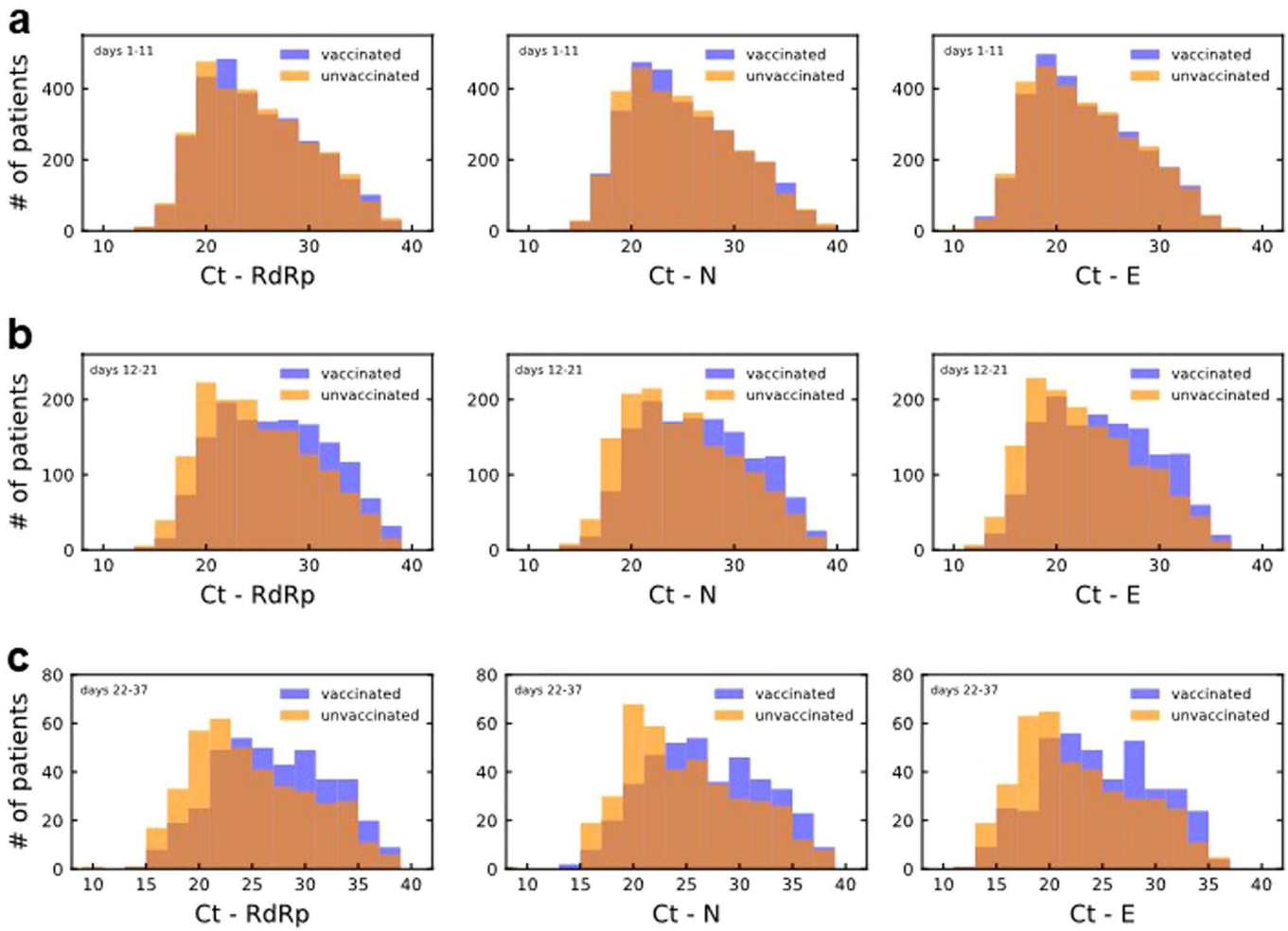




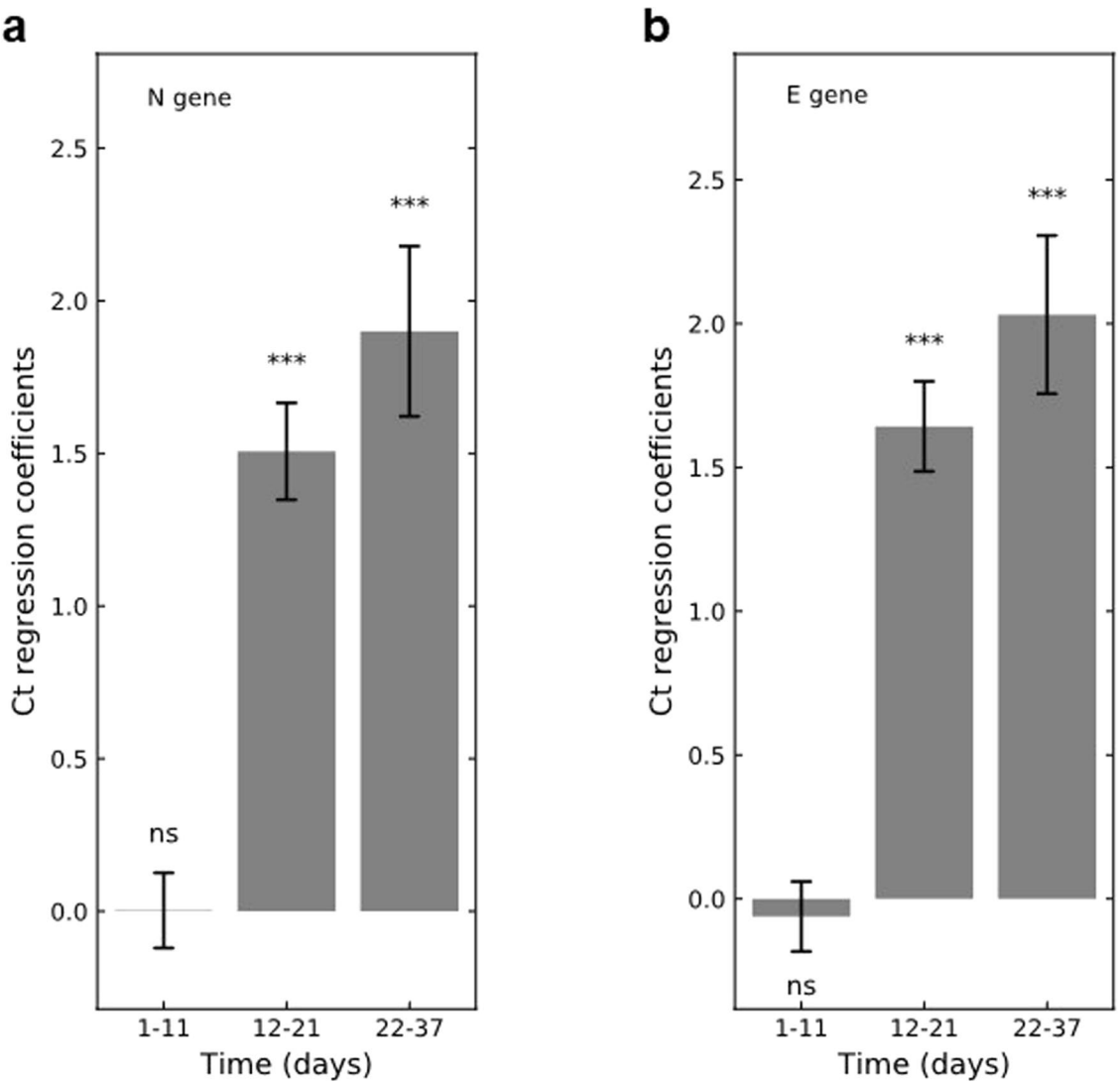
Extended Data Fig. 2 | Decreased SARS-CoV-2 viral load after 12 days post-vaccination. Mean Ct values of the N and E genes for positive tests following vaccination are plotted by the day the sample was taken (n = 4,938). Error bars indicate the standard error of the mean. For days 29-37 each dot represents the mean of 3 consecutive days. **a**, N gene. **b**, E gene. For RdRp gene see Fig. 1.



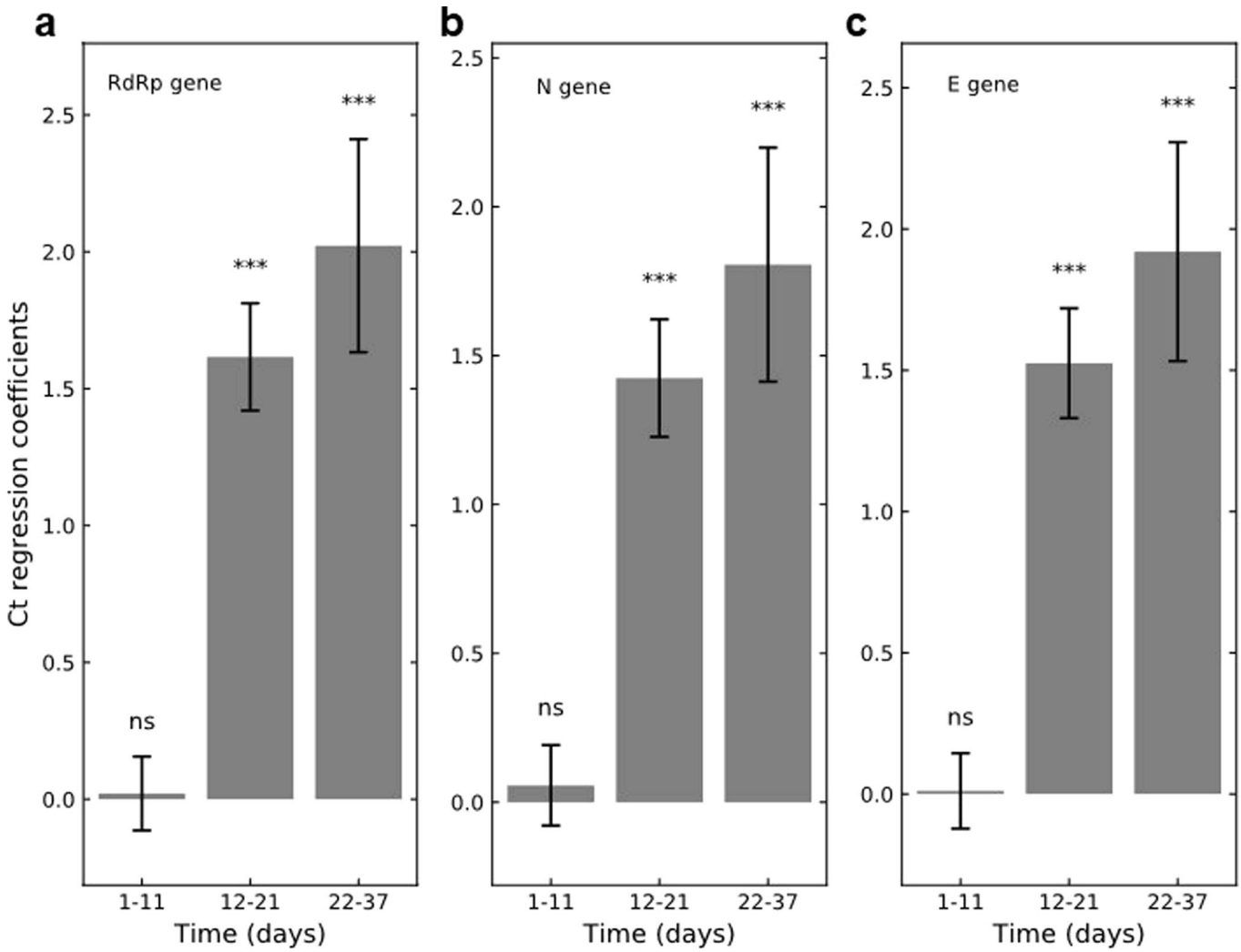
Extended Data Fig. 3 | Comparison of SARS-CoV-2 viral loads among patients vaccinated prior to positive sample and unvaccinated patients. The distribution of Ct values of viral genes as determined for positive samples taken either 1-11 days post-vaccination (n = 3,050, blue, top panels) or 12-37 days post vaccination (n = 1,888, blue, bottom panels) with their respective demographically-matched control groups (orange, *** - P-value < 10^{-10}, two-sided Mann-Whitney U test). **a**, 1-11 days post-vaccination. **b**, 12-37 days post-vaccination. For RdRp gene see Fig. 2a,b.



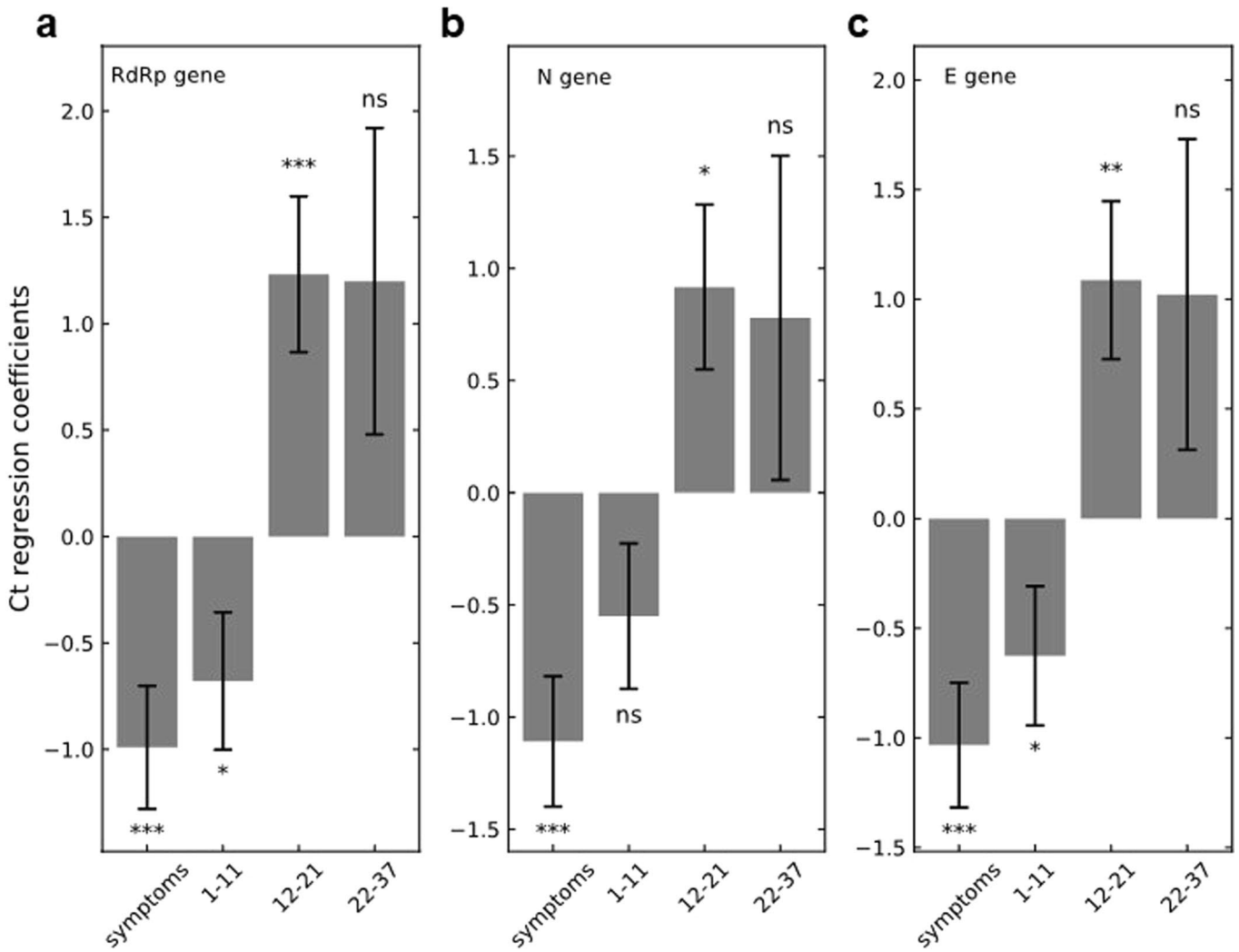
Extended Data Fig. 4 | SARS-CoV-2 viral load distribution for vaccinated and unvaccinated patients. The distribution of Ct values of viral genes as determined for positive samples taken a, 1-11 days post-vaccination with standard deviation of 5.27 ± 0.07, 5.27 ± 0.07 and 5.19 ± 0.07 (n = 3,050), **b**, 12-21 days post-vaccination with standard deviation of 5.39 ± 0.10, 5.39 ± 0.10 and 5.33 ± 0.10 (n = 1,486) and **c**, 22-37 days post-vaccination with standard deviation of 5.38 ± 0.19, 5.47 ± 0.19 and 5.37 ± 0.19 (n = 402) for RdRp, N and E genes respectively.



Extended Data Fig. 5 | Viral load is negatively associated with vaccination starting 12 days post-vaccination. The coefficient for the association of Ct of viral genes with time of vaccination in comparison to unvaccinated patients as identified in a single multivariable linear regression analysis accounting for age and sex (Methods,n = 9,876). Error bars represent one standard deviation. * - P-value < 0.05, ** - P-value < 0.01, *** - P-value < 0.001. **a**, N gene, **b**, E gene. For RdRp gene see Fig. 2c.



Extended Data Fig. 6 | Viral load is associated with vaccination also when applying an independent model for each time bin. The coefficient for the association of Ct of viral genes with time of vaccination in comparison to unvaccinated patients as identified in multivariable linear regression analyses accounting for age and sex for each time bin independently (Methods, n = 9,876). Error bars represent one standard deviation. * - P-value < 0.05, ** - P-value < 0.01, *** - P-value < 0.001. **a**, RdRp, **b**, N gene, **c**, E gene.



Extended Data Fig. 7 | Viral load is associated with vaccination when also accounting for symptomatic infections. The coefficient for the association of Ct of viral genes with time of vaccination in comparison to unvaccinated patients as identified in a single multivariable linear regression analysis accounting for age, sex and referral by symptoms for both vaccinated (symptomatic, n = 523; asymptomatic, n = 260) and unvaccinated (symptomatic, n = 534; asymptomatic, n = 249) patients (Methods). Error bars represent one standard deviation. * - P-value < 0.05, ** - P-value < 0.01, *** - P-value < 0.001. **a**, RdRp, **b**, N gene, **c**, E gene.

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Last updated by author(s): Mar 4, 2021

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

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Data collection	SQL query.
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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size was not restricted. It was only limited by the number of patients with available positive post-vaccination RT-qPCR test data.
Data exclusions	We have excluded patients above 90 years old of age. Since our analysis required matching unvaccinated patients for each vaccinated one with several conditions, we could not find matched patients for this small age group.
Replication	We report the results of an observational study.
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☒	☐ Animals and other organisms
☐	☒ Human research participants
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Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	Population is described in Extended Data Table 1.
Recruitment	This is an observational study involving electronic health records analysis.
Ethics oversight	Ethics committee of Maccabi Healthcare Services. IRB: 0066-20-MHS.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

CORRESPONDENCE

Effect of Vaccination on Household Transmission of SARS-CoV-2 in England

TO THE EDITOR: Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) prevents infection and reduces the severity of coronavirus disease 2019 (Covid-19) in vaccinated persons.[1,2] We investigated whether vaccination would reduce transmission in the household setting in the context of postvaccination infection.

We analyzed data from the Household Transmission Evaluation Dataset (HOSTED), which has information on all laboratory-confirmed cases of Covid-19 in England and in which data on all persons sharing the same address are linked.[3] We then linked to individual-level data on all Covid-19 vaccinations in England (see the Methods section in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

We compared the risk of secondary infection (defined as a positive SARS-CoV-2 test 2 to 14 days after the positive test for the index case) among unvaccinated household contacts of persons with SARS-CoV-2 infection who had received at least one dose of the ChAdOx1 nCoV-19 or BNT162b2 vaccine 21 days or more before testing positive with the risk among unvaccinated household contacts of unvaccinated persons with infection. We fitted logistic-regression models with adjustment for the age and sex of the person with the index case of Covid-19 (index patient) and the household contact, geographic region, calendar week of the index case, deprivation (a composite score of socioeconomic and other factors), and household type and size. We also considered the timing of effects among index patients who had been vaccinated at any time up to the date of the positive test.

Between January 4 and February 28, 2021, there were 960,765 household contacts of unvaccinated index patients, and there were 96,898 secondary cases of Covid-19 (10.1%). (Descriptive data regarding the index patients and their household contacts are provided in the Summary Results section.) The numbers of secondary cases according to the vaccination status of the index patient, and the results of logistic-regression models, are shown in Table 1. Overall, the likelihood of household transmission was approximately 40 to 50% lower in households of index patients who had been vaccinated 21 days or more before testing positive than in households of unvaccinated index patients; the findings were similar for the two vaccines. Most of the vaccinated index patients in our data set (93%) had

Table 1. Numbers of Household Contacts and Secondary Cases of Covid-19, According to Vaccination Status of Index Patient, and Adjusted Odds Ratios.*

Vaccination Status of Index Patient	Household Contacts	Secondary Cases	Adjusted Odds Ratio (95% CI)
	no.	*no. (%)*	
Not vaccinated before testing positive	960,765	96,898 (10.1)	Reference
Vaccinated with ChAdOx1 nCoV-19 vaccine ≥21 days before testing positive	3,424	196 (5.7)	0.52 (0.43–0.62)
Vaccinated with BNT162b2 vaccine ≥21 days before testing positive	5,939	371 (6.2)	0.54 (0.47–0.62)

* Odds ratios were adjusted for the age and sex of the index patient and their household contact, geographic region, calendar week of the index case, and an index of multiple deprivation and household type and size. CI denotes confidence interval, and Covid-19 coronavirus disease 2019.

received only the first dose of vaccine. Assessment of infection risks among household contacts according to the timing of vaccination of the index patient showed protective effects when the vaccine had been administered at least 14 days before the positive test (Figs. S1 and S2 in the Supplementary Appendix).

HOSTED does not include data on symptoms or cycle-threshold values and has information only on diagnosed cases. Among index patients, those who had been vaccinated were likely to be less severely symptomatic[2] and might have been less infectious than those who were unvaccinated.[4] Studies that involved active follow-up of contacts and that used serologic testing have shown higher rates of household transmission than were observed in our study[5]; bias could occur if case ascertainment differed between household contacts of vaccinated persons and those of unvaccinated persons. Our findings with respect to the timing of vaccination of index patients are consistent with previous data regarding the timing of individual protection after vaccination[1] and thus support the overall findings. There may have been misclassification of index and secondary cases, which are determined on the basis of testing dates; however, such misclassification would tend to attenuate the estimated protective effect of vaccination. Data are needed to inform the reduction in transmissibility of the virus after the receipt of two vaccine doses. It will be important to consider these findings alongside other emerging evidence to inform the benefits of vaccination.

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Drs. Dunbar and Dabrera contributed equally to this letter.

The Household Transmission Evaluation Dataset (HOSTED) surveillance system was reviewed and approved by the Public Health England Research Ethics Governance Group. The data were collected and linked by NHS Digital. The data were processed lawfully under General Data Protection Regulation Article 6(1)e and 9(2)i and shared under Regulation 3 of the Health Service (Control of Patient Information) Regulations 2002.

Supported by Public Health England.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on June 23, 2021, at NEJM.org.

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020; 383:2603-15.

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DOI: 10.1056/NEJMc2107717

Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study

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Running title: Delta VOC: Viral Kinetics for Vaccinated

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Keywords: COVID-19; SARS-CoV-2; breakthrough infection; delta; variants of concern; vaccine breakthrough; vaccination

Objectives

Highly effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed but variants of concerns (VOCs) with mutations in the spike protein are worrisome, especially B.1.617.2 (Delta) which has rapidly spread across the world. We aim to study if vaccination alters virological and serological kinetics in breakthrough infections.

Methods

We conducted a multi-centre retrospective cohort study of patients in Singapore who had received a licensed mRNA vaccine and been admitted to hospital with B.1.617.2 SARS-CoV-2 infection. We compared the clinical features, virological and serological kinetics (anti-nucleocapsid, anti-spike and surrogate virus neutralization titres) between fully vaccinated and unvaccinated individuals.

Results

Of 218 individuals with B.1.617.2 infection, 84 had received a mRNA vaccine of which 71 were fully vaccinated, 130 were unvaccinated and 4 received a non-mRNA. Despite significantly older age in the vaccine breakthrough group, the odds of severe COVID-19 requiring oxygen supplementation was significantly lower following vaccination (adjusted odds ratio 0.07 95%CI: 0.015-0.335, p=0.001). PCR cycle threshold (Ct) values were similar between both vaccinated and unvaccinated groups at diagnosis, but viral loads decreased faster in vaccinated individuals. Early, robust boosting of anti-spike protein antibodies was observed in vaccinated patients, however, these titers were significantly lower against B.1.617.2 as compared with the wildtype vaccine strain.

Conclusion

The mRNA vaccines are highly effective at preventing symptomatic and severe COVID-19 associated with B.1.617.2 infection. Vaccination is associated with faster decline in viral RNA load and a robust serological response. Vaccination remains a key strategy for control of COVID-19 pandemic.

Background

Availability of effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within one year of the first report of coronavirus disease 2019 (COVID-19) is remarkable. Phase 3 clinical trials of messenger RNA (mRNA) vaccines have demonstrated 92-95% efficacy in preventing symptomatic infection and severe disease [1-4] and intensive vaccination programs have reduced infection and mortality rates in multiple settings [5-7].

Emerging variants of concern (VOCs), such as B.1.1.7 (Alpha in the World Health Organization classification), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) exhibit varied sequence changes and alteration of amino acid sequences of the spike protein. This has led to concerns of viral immune evasion and decreased vaccine effectiveness. Furthermore, these VOCs have been shown to be more transmissible [8-10], and B.1.1.7 and B.1.617.2 has been associated with increased disease severity and hospitalization [11, 12]. B.1.617.2 has rapidly spread outside India, becoming the most frequently sequenced lineage worldwide by end of June 2021 [13]. Case series of vaccine-breakthrough infections have reported an over-representation by these VOCs [14, 15].

Understanding vaccine effectiveness in the context of VOCs requires granular data: which vaccines were administered, at what time point prior to infection, number of doses, and particularly which VOC has caused the infection. Important VOC-specific vaccination outcomes include severity of infection and vaccine effects on transmission.

The COVID-19 vaccination program was initiated in Singapore on 30 December 2020, with free vaccinations provided to all Singapore residents in phases, beginning with the elderly and those in high-risk occupations such as healthcare workers. Vaccines used are mRNA vaccines, Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273. As of 19 July 2021, 6,837,200 vaccine doses had been administered and ~2,792,430 individuals (47% of the total population) had completed the vaccination course [16]. In May 2021, B.1.617.2 became the dominant circulating variant based on local sequencing data.

In this multi-center cohort study, we characterize the clinical features, virological and serological kinetics of patients with vaccine-breakthrough PCR-confirmed B.1.617.2 infection and compared them with unvaccinated patients.

Methods

Patient Recruitment

Adults aged ≥18 years with COVID-19 confirmed by positive SARS-CoV-2 PCR and admitted to any of the five study sites from 1 April to 14 June 2021 were screened. Patients with B.1.617.2 infection (identification methods delineated below) were included in this analysis. Vaccine-breakthrough infection was defined as PCR-confirmed COVID-19 with symptom onset or first positive PCR (whichever was earlier) ≥14 days following a second dose of BNT162b2 or mRNA-1273 vaccine. Incomplete vaccination was defined as receipt of one dose of these vaccines ≥14 days prior to symptom onset or first positive PCR. Patients who received non-mRNA vaccines or developed infection within 14 days after the first dose were excluded from this analysis. B.1.617.2 vaccine-breakthrough infections were compared with a retrospective cohort of unvaccinated patients with B.1.617.2 infection admitted to one study site.

Data Collection

Clinical and laboratory data were collected from electronic medical records using a standardized data-collection form [17]. Laboratory data including cycle threshold (Ct) values from SARS-CoV-2 RT-PCR assays and serological results from Elecsys® (Roche, Basel, Switzerland) Anti-SARS-CoV-2 chemiluminescent immunoassays [anti-nucleocapsid (anti-N) and anti-spike protein (anti-S)] and surrogate virologic neutralization test (sVNT) cPass™ (Genscript, NJ, USA) were recorded. cPass™ detects total neutralizing antibodies targeting the viral spike protein receptor-binding domain [18]. These tests were performed as part of routine clinical care.

Additional Serologic testing

Serum samples from a subset of vaccine-breakthrough patients who had separately consented for specimen collection were additionally tested with a newly developed multiplex-sVNT assay using the Luminex platform. Further details can be found in the supplementary information.

Viral RNA sequencing and VOC determination

SARS-CoV-2 PCR was performed using various commercially available assays in different clinical laboratories. As part of active genomic surveillance, whole genome sequencing (WGS) by National Public Health Laboratory is performed for all patients in Singapore with SARS-CoV-2 detected by RT-PCR with a Ct value less than 30. Pangolin COVID-19 Lineage Assigner and CoVsurver were used to assign lineage to each sequence. For individuals with PCR confirmed infection without available sequencing results, lineage was inferred based on epidemiological investigations by the Singapore Ministry of Health (MOH), and likely B.1.617.2 infections were included (i.e., clear epidemiologic link with patients with sequencing confirmed B.1.617.2 infection).

Clinical Management

All individuals with confirmed COVID-19 (including asymptomatic cases) in Singapore are admitted to hospital for inpatient evaluation and isolation. Individuals with pneumonia requiring supplemental oxygen are treated with intravenous remdesivir, while dexamethasone and other agents were reserved for progressive infections per national guidelines [19]. Disease severity was stratified into asymptomatic, mild (no pneumonia on chest radiography), moderate (presence of pneumonia on chest radiography), severe (requiring supplemental oxygen), or critical (requiring intensive care unit [ICU] admission or mechanical ventilation). Collection of clinical data was censored on discharge from hospital.

Statistical Analysis

For descriptive analysis, data were presented as median (interquartile range (IQR)) for continuous parameters and frequency (percentage) for categorical variables. Chi-square and Fisher's exact tests

were used to compared categorical variables, while for continuous variables, t-test was used for normal data and Mann-Whitney U test for non-normal data. For asymptomatic patients, the day of confirmatory COVID-19 diagnosis was denoted as day one of illness. For symptomatic patients, the day of symptom onset or the day of confirmatory COVID-19 diagnosis, whichever earlier, was denoted as day one of illness.

Previously reported risk factors for disease severity [20] were evaluated and included in a multivariate logistic regression model [21]. For serial Ct values, we fitted a generalized additive mixed model (GAMM) with a random intercept by patient. To investigate the effect of vaccination status on rate of increase of Ct value, we included fixed factors of vaccination status and day of illness with smoothing terms and interaction between these two fixed factors. We plotted Ct values with marginal effect of day of illness by vaccination status and 95% confidence intervals (CI) from the GAMM.

For analysis of cPass™ and anti-S titres we fitted a GAMM to serial titres with random intercept by patient in addition to fixed factor of day of illness with smoothing terms, separately for vaccine-breakthrough and unvaccinated patients infected with Delta variant. We plotted cPass™/anti-S titres with marginal effect of day of illness and 95%CI from GAMM for each group of vaccine-breakthrough and unvaccinated patients.

P-values less than 0.05 were considered statistically significant, and all tests were 2-tailed. Data analyses were performed using Stata Release 15 (StataCorp, College Station, TX) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

Written informed consent was obtained from study participants of the multi-centre study approved by National Healthcare Group Domain Specific Review Board (NHG-DSRB) (Study Reference

2012/00917). Informed consent for retrospective data collection at National Centre for Infectious Diseases (NCID) was waived (NHG-DSRB reference number 2020/01122).

Results

218 B.1.617.2 infections were identified across the five study sites (Supplementary Figure S1). Of these, 71 met the definition for vaccine-breakthrough. An additional 13 only received one dose ≥14 days prior to disease onset or received both doses but within 14 days of disease onset, while four had received a non-mRNA vaccine overseas. Majority of participants meeting study definition for vaccine-breakthrough had received two doses of BNT162b2 (n=66, 93%).

Clinical Features

In line with Singapore's national vaccination strategy wherein older adults were prioritized for vaccination, our vaccine-breakthrough cohort was of significantly older age; median age of 56 years (IQR:39-64) versus 39.5 (IQR:30-58) ($p<0.001$) (Table 1). Other baseline demographics were similar.

Vaccine-breakthrough patients were significantly more likely to be asymptomatic (28.2% versus 9.2%, $p<0.001$); and if symptomatic, had fewer number of symptoms (Table 1). Unvaccinated individuals had worse levels of known biomarkers associated with increased COVID-19 severity including lymphocyte count, C-reactive protein [CRP], lactate dehydrogenase [LDH] and alanine transferase [ALT]. Correspondingly, a higher proportion of the unvaccinated cohort had pneumonia, required supplementary oxygen and ICU admission compared with the vaccinated cohort. A broader analysis comparing unvaccinated versus those who had received at least one dose of vaccine (i.e. both vaccine-breakthrough and incomplete vaccination) demonstrated similar findings (Supplementary Table T1).

Multivariate logistic regression analysis for development of severe COVID-19 (defined by supplementary oxygen requirement) demonstrated that vaccination was protective with an adjusted odds ratio (aOR) of 0.073 (95% confidence interval [CI]):0.016-0.343) ($p=0.001$) (Table 2). Analysis

comparing unvaccinated versus those who had received at least one dose of vaccine demonstrated similar findings (Supplementary Table T2). Multivariate logistic regression analysis for development of moderately severe COVID-19 (defined by development of pneumonia) also demonstrated that vaccination was protective with aOR of 0.069 (95%CI:0.027-0.180) (p<0.001) (Supplementary Table T3).

Virologic kinetics

Serial Ct values of individuals were analyzed as a surrogate marker for the viral load. The initial median initial Ct value did not differ between unvaccinated and fully vaccinated patients (unvaccinated median Ct 18.8 (14.9-22.7), vaccinated 19.2 (15.2-22.2), p=0.929). However, fully vaccinated patients had a faster rate of increase in Ct value over time compared with unvaccinated individuals, suggesting faster viral load decline (coefficient estimates for interaction terms ranged from 9.12 (standard error 3.75) to 12.06 (standard error 3.03); p-value <0.05 for each interaction terms) (Figure 1).

Serologic data

69 fully vaccinated individuals and 45 unvaccinated had serologic data available on record. 66/66 (100%) of vaccinated individuals had detectable S antibodies in week 1 of illness, while 7/45 (16%) of unvaccinated individuals did (Supplementary Figure S2). There was no difference in the proportion of individuals who seroconverted with the anti-N assay in week 1 (vaccinated 7/68 (10%) vs unvaccinated 11/107 (10%)) or week 2 (vaccinated 2/11 (18%), unvaccinated 4/20 (20%).

Analysis of sVNT with cPass indicated very high inhibition among vaccinated individuals in week 1 of illness (median 98.3% (IQR:91.0-99.4%)) which increased to 99.6% (IQR 99.3-99.9%) in week 2 (Figure 2A, 2B). Among unvaccinated individuals, median inhibition was below the 20% threshold at both week 1 and week 2. Among the 37 vaccinated individuals with a serum sample available for

testing by the multiplex sVNT assay, titres were significantly higher against wildtype virus compared with B.1.617.2 and other VOCs (Figure 3). sVNT titres were lowest against B.1.617.2 and P.1 VOCs.

Discussion

In this study, we found that fully vaccinated patients had significantly lower odds of moderate or severe outcomes following infection by the SARS-CoV-2 VOC B.1.617.2. Vaccination was associated with lower peak measures of systemic inflammation, fewer symptoms, including more asymptomatic infection, and better clinical outcomes. Notably, in contrast to existing studies that showed lower viral load in vaccinated patients [22], initial viral load indicated by PCR Ct values was similar between vaccinated and unvaccinated patients with B.1.617.2. However, vaccinated patients appeared to clear viral load at a faster rate. Our serologic data suggest an early rapid rise in neutralizing and binding antibodies indicated by C-Pass and Roche anti-S antibodies, which may be evidence of memory immunity to COVID-19 vaccination on challenge with a breakthrough infection with B.1.617.2.

As part of active case finding and surveillance in Singapore, all patients with fever or respiratory symptoms, close contacts of confirmed cases, and newly arrived travelers are screened for COVID-19 using PCR. Additionally, high-risk individuals in frontline occupations or congregate settings are tested as part of routine surveillance. All confirmed COVID-19 cases are reported to MOH and admitted to a hospital for initial evaluation. As such, our hospitalized cohort uniquely captures the entire spectrum of disease severity of COVID-19 infection and provides granular data even for mild and asymptomatic vaccine-breakthrough infections, giving us the opportunity to analyze virologic and serologic kinetics of these patients.

The finding of diminished severity with B.1.617.2 infection in vaccinated individuals is reassuring and corroborates emerging data from the United Kingdom which have found that mRNA vaccination remains protective against symptomatic and severe disease[12, 23]. An observational cohort study conducted in Scotland suggested that ≥14 days after the second dose, BNT162b2 vaccine offered

92% vaccine effectiveness against presumptive non-B.1.617.2 infection and 79% protection against presumptive B.1.617.2 [24]. Protection associated with the ChAdOx1 nCoV-19 vaccine was 73% and 60% respectively. Although vaccine-breakthrough infections are increasingly reported, with the largest series to date in the United States reporting 10,262 breakthrough infections, a majority of these were mild (27% asymptomatic, 10% hospitalization, 2% mortality)[25]. Vaccine-breakthrough infections will continue to be observed, especially with genetic drift and selection pressures resulting in emergence of newer VOCs; however, it is likely that there will be a shift toward milder disease spectrum with more widespread implementation of vaccination programs.

To our knowledge, we provide the first data characterizing impact of vaccination on virologic kinetics by the B.1.617.2 variant. While initial Ct values were similar; the effect of vaccination with a more rapid decline in viral load (and hence shorter duration of viral shedding) has implications on transmissibility and infection control policy. A shorter duration of infectivity may allow a shorter duration of isolation for vaccinated individuals. Based on our data, it seems likely that vaccination reduces secondary transmission, though this needs to be further studied in larger community surveillance studies. Other studies found similar impact of vaccination on other variants. Pritchard and colleagues found that vaccinated individuals had higher Ct values compared with unvaccinated individuals in B.1.1.7 infections [7], while Levine-Tiefenbaum and colleagues similarly found a reduction in viral loads after BNT162b2 vaccine, though no data was provided on variant type [26].

There are several limitations to our study. Firstly, we only compared vaccine-breakthrough infections with unvaccinated COVID-19 patients. We did not study vaccinated individuals who had similar exposure risk but did not develop COVID-19 infection. We thus could not evaluate vaccine efficacy against asymptomatic infection. We also did not have detailed epidemiologic data to study the effect of vaccination on preventing secondary transmission.

Secondly, we could only obtain serologic tests after infection since patients were recruited after confirmation of infection. While active contact tracing and case finding in Singapore resulted in early

identification of most COVID-19 cases, the first available serologic result was at a median of 2 (IQR:1-3) days of illness and antibody levels are likely to already have been boosted by natural infection. We thus could not evaluate the underlying immunologic mechanisms behind vaccine-breakthrough infection, e.g., diminished neutralizing antibody level or impaired cellular immunity. Further study should compare similarly exposed vaccinated individuals who develop breakthrough infection with those who do not, to elucidate the underlying drivers of susceptibility, which may enlighten us on how to optimize protection (e.g., through enhanced/boosted dosing schedules).

Thirdly, PCR testing was not standardized in a centralized laboratory, and instead conducted at each centre using different validated commercial assays. Ct values are only a surrogate measure of viral load and shedding. We did not evaluate viability of shed virus via viral culture. In addition, we only evaluated participants with mRNA vaccination, and thus our findings are restricted to mRNA vaccines and not all COVID-19 vaccines.

Conclusion

mRNA vaccines against COVID-19 are protective against symptomatic infection and severe disease by the B.1.617.2 variant. Vaccinated individuals had a more rapid decline in viral load, which has implications on secondary transmission and public health policy. Rapid and widespread implementation of vaccination programs remains a key strategy for control of COVID-19 pandemic. Further studies should elucidate immunologic features driving vaccine-breakthrough infection to improve vaccine-induced protection.

Conflict of Interest Disclosures

BEY reports personal fees from Roche and Sanofi, outside the submitted work. All other authors declare no competing interests.

Acknowledgments

We thank all clinical and nursing staff who provided care for the patients and staff in the Infectious Disease Research and Training Office of the National Centre for Infectious Diseases who assisted with data collection. We will also like to thank Jeremy Cutter at the National Public Health and Epidemiology Unit of National Centre for Infectious Diseases who assisted with data management on Ct values.

Funding

This study was funded by grants from the Singapore National Medical Research Council (COVID19RF-001, COVID19RF-008). The funders had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

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	Unvaccinated n = 130	Vaccinated n = 71	*p*-value
Median age (IQR), years	39.5 (30-58)	56 (39-64)	<0.001
Male (%)	67 (51.5)	27 (38)	0.067
Median Charlson Comorbidity Index (IQR)	0 (0-1)	0 (0-0)	0.125
Diabetes mellitus (%)	28 (21.5)	5 (7.0)	0.008
Hypertension (%)	28 (21.5)	14 (19.7)	0.762
Hyperlipidaemia (%)	32 (24.6)	18 (25.4)	0.908
Median Ct value on diagnosis (IQR)*	18.8 (14.9-22.7)	19.2 (15.2-22.2)	0.929
Asymptomatic	12 (9.2)	20 (28.2)	<0.001
Symptom onset after Diagnosis (%)	11 (9.3)	11 (21.6)	0.030
Median day of illness symptoms start (IQR)	2 (2-3)	3 (2-3)	0.715
Median Ct values for Symptom Onset After (IQR)	21.87 (18.8-31.2)	19.2 (16.6-21.5)	0.279
Median Sum of Symptoms Reported (IQR)	2 (1-3)	1 (0-2)	<0.001
Fever (%)	96 (73.9)	29 (40.9)	<0.001
Cough (%)	79 (60.8)	27 (38)	0.002
Shortness of Breath (%)	17 (13.1)	1 (1.4)	0.004
Runny Nose (%)	31 (23.9)	27 (38)	0.034
Sore Throat (%)	43 (33.1)	18 (25.4)	0.255
Diarrhoea (%)	8 (6.2)	0	0.052
Median highest Neutrophil (IQR) $\times 10^9$/L	4.50 (3.07-5.92)	4.33 (3.52-5.43)	0.117
Median lowest Lymphocyte (IQR) $\times 10^9$/L	0.95 (0.65-1.50)	1.36 (1.02-1.87)	<0.001
Median highest C-Reactive Protein (IQR), mg/L	24.7 (6.9-84.8)	12.6 (6.5-22.5)	<0.001
Median highest Lactate Dehydrogenase (IQR), U/L	486 (365-672)	373 (314-421)	0.062
Median highest Alanine Transferase (IQR), U/L	35	19	<0.001

	(18-74)	(13-34)	
Disease Outcome			
Pneumonia (%)	69 (53.1)	9 (21.7)	<0.001
Supplementary O2 required (%)	27 (20.8)	2 (2.8)	<0.001
ICU admission required (%)	7 (5.4)	0	0.053
Median days of ICU admission required (IQR)	4 (3-9)	-	-
Intubation (%)	2 (1.5)	0	0.541
Median days of Intubation (IQR)	7 (3-11)	-	-
COVID-19 specific treatment (%)	39 (30)	5 (7)	<0.001
Mortality	2 (1.54)	0	0.541

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290 Table 1: Baseline characteristics and disease outcome between unvaccinated and completed mRNA

291 vaccination COVID-19 B1.617.2 infected patients

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	Univariable model		Multivariable model	
	Crude OR (95% CI)	***p*-value**	**Adjusted OR (95% CI)**	***p*-value**
Vaccinated	0.111 (0.025-0.480)	0.003	0.073 (0.016-0.343)	0.001
Age group				
<45 years old	1	-	1	-
45-64 years old	6.19 (1.90-20.2)	0.003	8.29 (2.29-30.0)	0.001
>64 years old	13 (3.90-42.9)	<0.001	13.5 (2.66-68.8)	0.002
Male	0.913 (0.414-2.01)	0.821	1.09 (0.418-2.85)	0.857
Diabetes	6.18 (2.59-14.7)	<0.001	2.24 (0.785-6.41)	0.132
Hypertension	4.8 (2.09-11.0)	<0.001	1.62 (0.509-5.18)	0.413
Presence of other comorbidities, if any	3.96 (1.66-9.44)	0.002	0.897 (0.262-3.07)	0.862

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294 **Table 2:** Odds ratio of candidate risk factors for development of severe COVID-19 for completed

295 mRNA vaccination COVID-19 B1.617.2 infected patients. CI, confidence interval; OR, odds ratio

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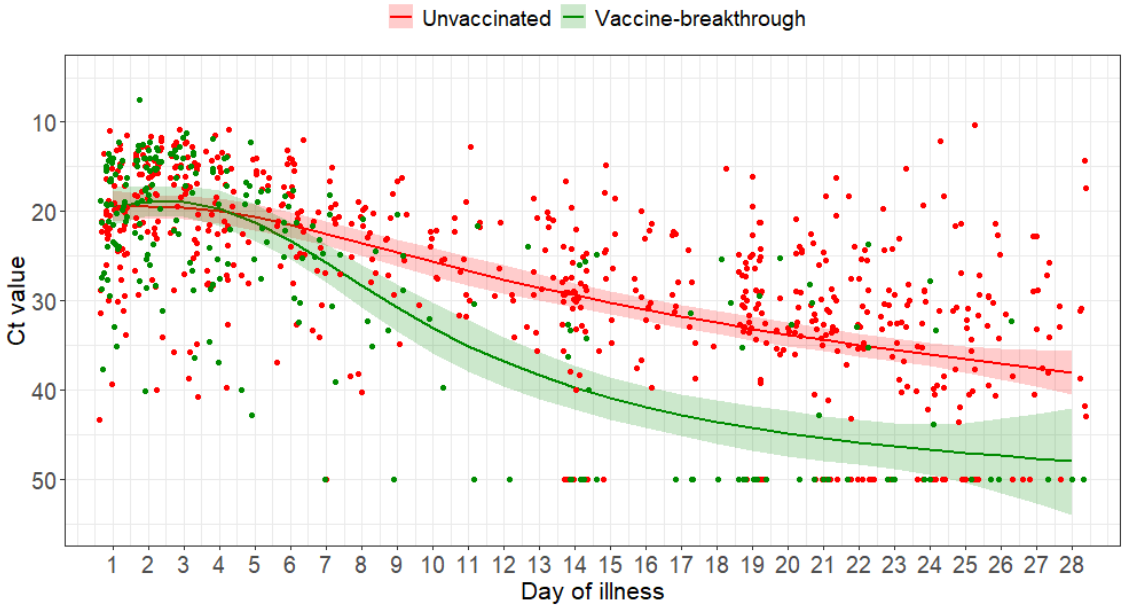

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299 **Figure 1:** Scatterplot of Ct values and marginal effect of day of illness of COVID-19 B1.617.2 infected

300 patients with 95% confidence intervals from generalized additive mixed model with interaction term

301 between vaccination status and day of illness

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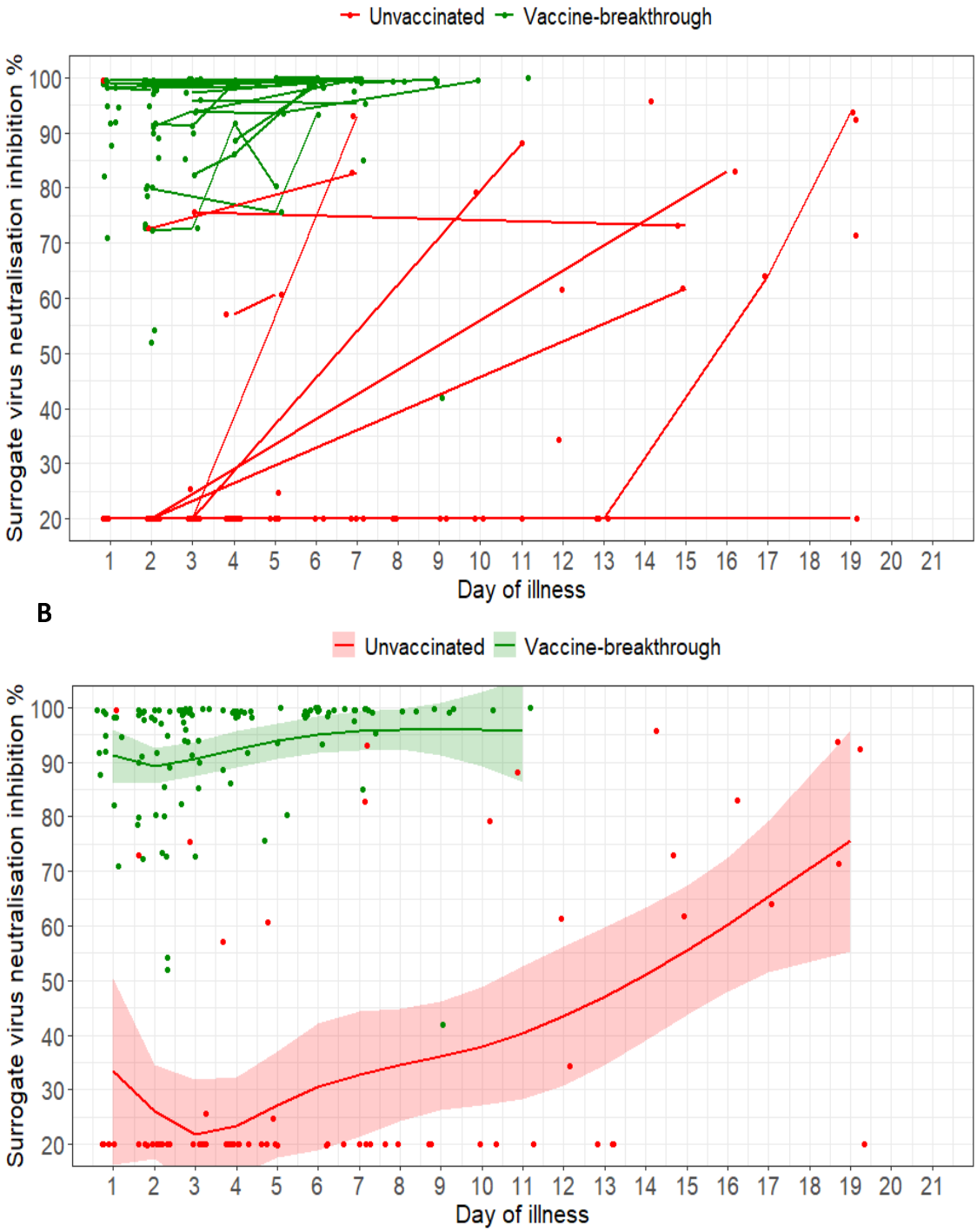

Figure 2: (A) Spaghetti plot of surrogate virus neutralisation (sVNT) inhibition % as measured by cPass; (B) Scatterplot of sVNT inhibition % and marginal effect of day of illness by vaccine-breakthrough and unvaccinated groups of COVID-19 B1.617.2 infected patients with 95% confidence

313 intervals from generalized additive mixed models. For both plots, n=127; vaccine-breakthrough = 67,

314 unvaccinated = 60

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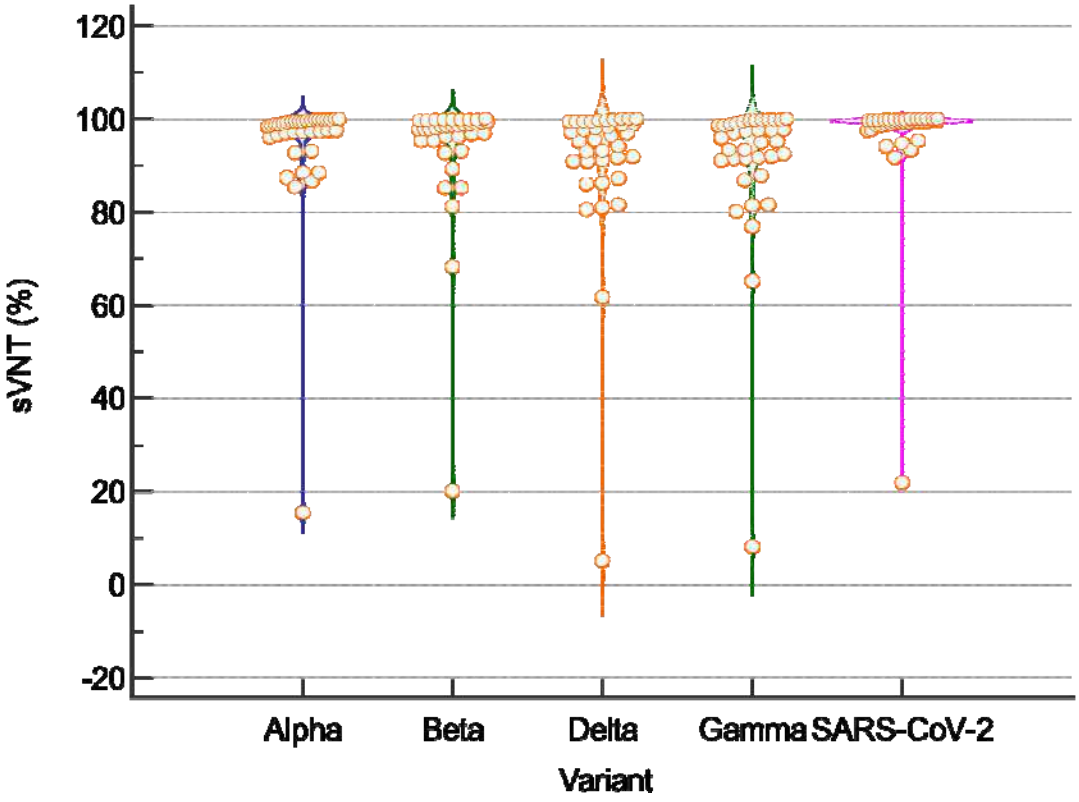

317

318 **Figure 3:** Violin plots of of surrogate virus neutralisation (sVNT) inhibition % against wildtype SARS-

319 CoV-2 and the B.1.617.2 variant for 36 patients with vaccine-breakthrough infection (median day of

320 sample collection from infection onset 6 days (inter-quartile range (IQR) 3-7). Titres against the four

321 variants were significantly lower than against wildtype SARS-CoV-2 [median sVNT, B.1.1.7 98.5%

322 (IQR: 96.3-99.5); B.1.351 98.2% (IQR: 95.3-99.5); B.1.617.2 96.0% (IQR: 90.9-99.3); P.1 95.5% (IQR:

323 91.3-98.9); Wildtype 99.4% (IQR: 98.5-99.7), Kruskal-Walis p-value = 0.00055, Post-hoc pairwise

324 comparison (Conover) Wildtype versus each variant $p<0.05$]

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